International Union of Basic and Clinical Pharmacology. LXXVIII. Lysophospholipid Receptor Nomenclature

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Abstract

Lysophospholipids are cell membrane-derived lipids that include both glycerophospholipids such as lysophosphatidic acid (LPA) and sphingoid lipids such as sphingosine 1-phosphate (S1P). These and related molecules can function in vertebrates as extracellular signals by binding and activating G protein-coupled receptors. There are currently five LPA receptors, along with a proposed sixth (LPA1-LPA6), and five S1P receptors (S1P1-S1P5). A remarkably diverse biology and pathophysiology has emerged since the last review, driven by cloned receptors and targeted gene deletion (“knockout”) studies in mice, which implicate receptor-mediated lysophospholipid signaling in most organ systems and multiple disease processes. The entry of various lysophospholipid receptor modulatory compounds into humans through clinical trials is ongoing and may lead to new medicines that are based on this signaling system. This review incorporates IUPHAR Nomenclature Committee guidelines in updating the nomenclature for lysophospholipid receptors (http://www.iuphar-db.org/DATABASE/FamilyMenuForward?familyId=36).

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This article is available online at http://pharmrev.aspetjournals.org. doi:10.1124/pr.110.003111.
I. Introduction

Lysophosphatidic acid (LPA\(^1\)) and sphingosine 1-phosphate (SIP) are phospholipids derived from the cell membrane that also act as extracellular signals in vertebrates. Over the last decade, a consensus has emerged that most major extracellular actions of these lipids are mediated by predicted 7-transmembrane domain, G protein-coupled receptors (GPCRs). The identification of cognate receptors for LPA (Hecht et al., 1996) and SIP (Lee et al., 1998) has opened the door to the cloning of related genes, referred to initially as endothelial differentiation genes (EDGs), that encode for eight of the accepted lysosphospholipid receptors. In addition, other GPCR genes with lesser homology have also been identified as LPA receptors (Noguchi et al., 2003; Kotarsky et al., 2006; Lee et al., 2006). The latter genes are more closely related to the family of P2Y purinergic receptor genes, indicating that LPA receptors have evolved through two distinct lineages in the rhodopsin GPCR family. A remarkable extent of heterogeneity for receptor subtypes, gene expression patterns, and effector pathways has underscored the diverse biological potential of receptor-mediated lysosphospholipid signaling. This expectation has been met through studies of receptor knockout mice that have been reported for most of the identified receptors (Choi et al., 2008; Lee et al., 2008). The production of potent agonists and antagonists for some of these receptors has provided new insights into the therapeutic potential of this signaling system, the most prominent example being FTY720 (fingolimod), a sphingosine analog that, upon phosphorylation, becomes a receptor nonselective agonist at four of five S1P receptors (Chun and Hartung, 2010). In September 2010, fingolimod received U.S. Food and Drug Administration approval, with the commercial name Gilenya, in view of the results from two phase III clinical trials, as a first-line therapy for relapsing-remitting multiple sclerosis (Cohen et al., 2010; Kappos et al., 2010).

More receptor-related details, as well as review of important enzymological mechanisms involved in ligand production, can be found in recent reviews on LPA receptors (Anliker and Chun, 2004; Ishii et al., 2004; Chun, 2005; Herr and Chun, 2007; Choi et al., 2008; Rivera and Chun, 2008; Noguchi et al., 2009; Skoura and Hla, 2009; Teo et al., 2009; Choi et al., 2010), LPA enzymeology (Moolenaar et al., 2004; Aoki et al., 2008), and S1P receptors (Saba, 2004; Chun, 2005; Kono et al., 2008; Rivera et al., 2008; Maceyka et al., 2009; Skoura and Hla, 2009). This review focuses primarily on updating the IUPHAR nomenclature for the currently recognized lysospholipid receptors, all of which are GPCRs.

II. Lysosphospholipid Receptor Nomenclature

The currently accepted group of lysospholipid receptors for LPA (along with the proposed addition of LPA\(_x\)) and SIP are noted (Table 1). Receptor protein names are referred to as LPA\(_x\), with \(x = 1\) to 6, or SIP\(_x\), with \(x = 1\) to 5. Gene names in the literature include the original orphan names, especially “EDG,” with current functional gene names used by the Human Genome Organization nomenclature committee (http://www.hugo-international.org/index.php) for human genes and the Mouse Genome Informatics (http://www.informatics.jax.org/) gene names for murine species. The Human Genome Organization names are LPAR\(_x\) or S1PR\(_x\), whereas Mouse Genome Informatics names are Lpar\(_x\) and S1pr\(_x\), with \(x = 1\) to 6 for LPA receptor genes and \(x = 1\) to 5 for SIP receptor genes. In addition to the discovery of new LPA receptors since the last review, two reports on putative receptors for the lysospholipids sphingosylphosphorylcholine (Xu et al., 2000) and lysophosphatidylcholine (Kabarowski et al., 2001) have been retracted (Witte et al., 2005; Xu et al., 2006). For simplicity, receptor names will be used herein along with an indication of the species from which data were obtained. A summary of receptor names, gene names, and related information is presented in Table 1.

A. Lysosphosphatidic Acid Receptors

There are currently five bona fide, high-affinity cognate GPCRs for lysosphosphatidic acid (LPA\(_1\)–LPA\(_5\)) along with a proposed 6th receptor, LPA\(_6\). There may be other receptors as well; therefore, this group should be considered a work in progress. Since the last IUPHAR Nomenclature Report (Chun et al., 2002), the three new LPA receptors that have been added are numbered based upon the date of their initial report, independent validation, and IUPHAR committee consensus: LPA\(_1\) to LPA\(_6\). Additional details on LPA receptor knockouts, biological and pathophysiological aspects, along with additional chemical tools, can be found elsewhere (e.g., Choi et al., 2010).
1. **LPA1**. This was the first lysophospholipid receptor to be functionally identified (Hecht et al., 1996; for review, see Fukushima et al., 2001; Ishii et al., 2004). It was known previously by orphan names VZG-1, EDG-2, mrec1.3, and lpA1. The human gene for LPA1 encodes a ~41-kDa protein of 364 amino acids. It interacts with the heterotrimeric G proteins \(G_{i/o}, G_{q/11}, \) and \(G_{12/13}\) (Fukushima et al., 1998; Ishii et al., 2000). Constitutive gene deletion in mice (Contos et al., 2000a,b, 2002) has revealed association with a wide range of developmental effects, particularly in the central nervous system (CNS) (Contos et al., 2000a,b; Kingsbury et al., 2003; Estivill-Torrués et al., 2008; Matas-Rico et al., 2008; Santin et al., 2009; Castilla-Ortega et al., 2010; Dubin et al., 2010), as well as organismal survival (50% perinatal death; Contos et al., 2000a,b, 2002), and receptor loss has been linked to multiple disease processes including cancer (Hama et al., 2004), the initiation of neuropathic pain (Inoue et al., 2004, 2006, 2008), fibrosis in kidney (Pra`dere et al., 2007) and lung (Tager et al., 2008), and male infertility (Ye et al., 2008), in conjunction with loss of other LPA receptors.

2. **LPA2**. LPA2 is a receptor with ~60% amino acid similarity to LPA1, with a predicted amino acid sequence of 348 amino acid residues and molecular mass of 39 kDa (An et al., 1998; Contos et al., 2000a,b). Prior names include EDG-4 and lpA2. This receptor interacts with heterotrimeric G proteins \(G_{i/o}, G_{11/q}, \) and \(G_{12/13}\). Constitutive receptor loss in mice produces a grossly normal phenotype; however, this receptor contributes to LPA signaling in the developing nervous system (Kingsbury et al., 2003; Dubin et al., 2010), synaptic functions in the adult CNS (Trimbuch et al., 2009), and effects on the male reproductive system (Ye et al., 2008), on the basis of the combined deletion of multiple LPA receptors, and has also been linked to some forms of cancer (Lin et al., 2009) and lung function in asthma (Zhao et al., 2009).

3. **LPA3**. LPA3, formerly known as EDG-7 and lpA3 (Bandoh et al., 1999; Im et al., 2000b; Fukushima et al., 2001) is a 40 kDa GPCR that in mouse is 50% identical in amino acid sequence to LPA1 and LPA2. As with LPA1 and LPA2, it can couple with \(G_{i/o}\) and \(G_{q}\). It is more potently activated by 2-acyl-LPA with unsaturated fatty acids (Bandoh et al., 1999; Sonoda et al., 2002). Constitutive loss of LPA3 in mice results in delayed and abnormal embryo implantation in the uterus (Ye et al., 2005; Hama et al., 2007) and contributes to male infertility in conjunction with LPA1 and LPA2 (Ye et al., 2008). Influences on dendritic cell chemotaxis have also been reported (Chan et al., 2007).

4. **LPA4**. LPA4 was an orphan receptor referred to as GPR23, p2y9, and p2y5-like (Janssens et al., 1997; O’Dowd et al., 1997). It was the first dissimilar LPA receptor to be identified, compared with the eight previously identified lysophospholipid receptors, and is located on the X chromosome (Noguchi et al., 2003). It has 370 amino acids with a predicted molecular mass of ~42
kDa (Janssens et al., 1997; O’Dowd et al., 1997) and couples to G_{12/13}, G_{q/11}, G_i, as well as G_{o} (Lee et al., 2007; Yanagida et al., 2009). Constitutive gene deletion in mice produces grossly normal animals with some reported defects on cell motility (Lee et al., 2008), as revealed in culture studies, whereas an independent study (Sumida et al., 2010) identified partially penetrant functions of homozygous deletion in embryonic blood and lymphatic vessel formation.

5. **LPA_6**. The orphan receptor gene GPR92 was shown to encode a 5th LPA receptor, now referred to as LPA_6 (Kotarsky et al., 2006; Lee et al., 2006). Human LPA_6 is composed of a 372-amino acid protein with a predicted molecular mass of ~41 kDa and shares ~35% homology with LPA_4 (Lee et al., 2006). It couples to G_{12/13} and G_{o} (Kotarsky et al., 2006; Lee et al., 2006). Farnesyl pyrophosphate and N-arachidonoylglycine were proposed as LPA_6 ligands (Oh et al., 2008). However, further independent studies indicated that LPA_6 is a legitimate LPA receptor (Williams et al., 2009; Yin et al., 2009). It has been proposed that LPA_6 is an alkyl (ether) LPA-preferring receptor (Williams et al., 2009). Ether LPAs, which are less potent than ester LPAs at LPA_4 to LPA_3, are clearly more potent at platelet aggregation. Constitutive gene deletion in mice has not been reported.

6. **LPA_\beta**. The committee generally supported the inclusion of the orphan receptor P2Y5 as LPA_\beta on the basis of the emerging literature (Pasternack et al., 2008; Lee et al., 2009; Yanagida et al., 2009); however, the atypical functions of this receptor in standard assays led most to recommend circumspection with this identity, which continues to be clarified. LPA_\beta is most closely related to LPA_4. Genetic studies also support the view that it encodes a functional LPA receptor, where it has been shown to influence forms of human hair growth (Pasternack et al., 2008; Shinkuma et al., 2010). Its gene structure is that of a nested gene within intron 17 of the retinoblastoma gene and encodes a 344-amino acid protein with a predicted molecular mass of ~39 kDa. LPA_\beta couples to G_{12/13} and G_\beta (Lee et al., 2009; Yanagida et al., 2009). It was reported that 2-acyl-LPA rather than 1-acyl-LPA is the preferred ligand of LPA_\beta (Yanagida et al., 2009). Constitutive deletion in mice has not been reported but would be expected to phenocopy major aspects of human receptor loss that affect forms of hair growth. It is noteworthy that homozygous inactivation of LPA_\beta has also been implicated in bladder cancer development through unclear mechanisms that may reduce the activity of the tumor suppressor gene, RB1 (Lee et al., 2007).

7. **Other Proposed Receptors**. Three other orphan GPCRs have been proposed as new LPA receptors: GPR87, P2Y10 (Tabata et al., 2007; Murakami et al., 2008; Pasternack et al., 2008), and GPR35 (Oka et al., 2010). A consensus was reached to exclude these putative LPA receptors from the current list of six LPA receptors, which could change in the future based upon further experimental validation. Non-GPCR LPA receptors have also been reported and require further validation (McIntyre et al., 2003).

**B. Sphingosine 1-Phosphate Receptors**

At the present time, there are a total of five bona fide apparent high-affinity cognate GPCRs for S1P (S1P_1–S1P_5). Since the last IUPHAR Nomenclature Report in 2002 (Chun et al., 2002), no new S1P receptors have been reported. All of the S1P receptors specifically bind both S1P, dihydro-S1P (also called sphinganine 1-phosphate), and phytoS1P (4-hydroxysphinganine 1-phosphate) with low nanomolar affinities. Other sphingolipids (such as sphingosylphosphorylcholine) may activate these receptors at very high (micromolar), generally nonphysiological concentrations, and there is no evidence yet for additional endogenous ligands.

1. **S1P_1.** S1P_1, previously named EDG-1, was the first S1P receptor to be functionally identified (Lee et al., 1998) [reviewed in (Fukushima et al., 2001; Ishii et al., 2004)]. Human S1P_1 contains a 381 amino acid that shares 94% sequence identity with the murine receptor. S1P_1 couples exclusively to G_\text{io}. Because S1P_1 activates the protein kinase Akt and the small GTPase Rac, activation of S1P_1 results in the formation of lamellapodia and cell-cell junctions (adherens junctions) (Lee et al., 1999, 2001).

Constitutive receptor loss results in embryonic lethality (Liu et al., 2000), affecting vasculature and nervous system development. S1P_1 was the first example of a lysophospholipid receptor that was required for embryonic development, and it plays a major role in angiogenesis and vascular development (Kono et al., 2004), neurogenesis (Mizugishi et al., 2005), and trafficking of lymphocytes, as well as other hematopoietic cells, on the basis of data from both constitutive and conditional mutants that have also been produced (Skoura and Hla, 2009). S1P_1 signaling under physiological homeostasis is needed for maintenance of basal permeability barriers of the vascular system. Administration of one class of pharmacological antagonists of S1P_1 led to marked increases in basal permeability of the mouse lung (Foss et al., 2006; Sanna et al., 2006). In myeloid cells, S1P_1 seems to be important for maintaining the expression of genes that mediate anti-inflammatory mechanisms (Hughes et al., 2008).

2. **S1P_2.** This receptor was previously known as EDG-5, H218, AGR16, and lpB2. It participates in S1P-induced cell proliferation, motility, and transcriptional activation, generally acting in opposition to S1P_1 (Skoura and Hla, 2009). Human S1P_2 contains 353 amino acids and is highly conserved across species. Although S1P_2 can couple to G_\text{io}, G_o, G_i, and G_{12/13}, it couples most efficiently to G_{12/13} and potently activates the small GTPase Rac (Gonda et al., 1999; Win dh et al., 1999; Okamoto et al., 2000).
Constitutive gene deletion has shown that although S1P2 is not necessary for normal development, this receptor cooperates with S1P1 during vascular development (Kono et al., 2004). Lack of S1P2 led to hearing and balance defects as a result of alterations in hair cells, support cells, and vasculature (stria vascularis) of the inner ear (Kono et al., 2007), although other mechanisms related to direct protection of hair cells likely also occur (MacLennan et al., 2006; Herr et al., 2007). S1P3 also promotes pathologic angiogenesis and retards normal vascularization in the retinas of mice during hypoxia-induced retinopathy [on the basis of loss-of-function in receptor-null animals (Skoura et al., 2007)] and, in conjunction with S1P3, can provide protection in myocardial ischemia-reperfusion models (Means et al., 2007). It has similarly been linked to reduced fertility, in conjunction with S1P3 loss (Ishii et al., 2002), as well as to hepatic wound healing, fibrosis, and regenerative capacity (Serriere-Lanneau et al., 2007; Ikeda et al., 2009).

3. S1P3: Human S1P3 contains 378 amino acids that are 92% homologous to the murine S1P3 receptor. It was previously known as EDG-3 and lpB3. Like S1P2, S1P3 can couple with G\textsubscript{q}, G\textsubscript{q}, and G\textsubscript{12/13} (Ancellin and Hla, 1999; Windh et al., 1999). However, it most efficiently couples to the G\textsubscript{q} protein and stimulates the hydrolysis of phosphatidylinositol bisphosphate, to form inositol 1,4,5-trisphosphate and thereby leading to intracellular Ca\textsuperscript{2+} increases and activation of protein kinase C. S1P3 binds S1P and dihydro-S1P with affinities in the 20 nM range (Van Brocklyn et al., 1999).

Constitutive deletion (Ishii et al., 2001) did not reveal a gross phenotype but did contribute to infertility in conjunction with S1P2 loss (Ishii et al., 2002). A clear role for S1P3 has also been demonstrated in the regulation of heart rate in rodents (Forrest et al., 2004; Sanna et al., 2004), and it has been shown to regulate lymphoid endothelial cells (Girkontaite et al., 2004) and to have effects on endothelial progenitor cells (Walter et al., 2007). S1P3 regulates myocardial perfusion and provides protection in ischemia-reperfusion injury (Lekvag et al., 2004; Theilmeier et al., 2006; Means et al., 2007) and further influences vasorelaxation (Nofer et al., 2004) and cardiac fibrosis (Takuwa et al., 2009). Other influences on myofibroblasts (Keller et al., 2007), as well as S1P3 links to PAR-1 signaling that couples coagulation events with inflammation (Niessen et al., 2008), have been reported. Numerous abstracts and presentation have documented that bradycardia in primates, including humans, is driven by S1P1, in that its expression is localized to myocytes and perivascular smooth muscle cells, and its activation results in bradycardia and hypertension.

4. S1P4: Human S1P4, previously known as EDG-6 and lpC1, contains 384 amino acids that share 82% sequence identity with the murine S1P4 receptor (Van Brocklyn et al., 2000). S1P4 couples to G\textsubscript{q}, G\textsubscript{q}, and G\textsubscript{12/13}. S1P4 has been reported to be primarily expressed in lymphoid tissues (Graeler and Goetzl, 2002) and mediates immunosuppressive effects of S1P by inhibiting proliferation and secretion of effector cytokines (Wang et al., 2005). Null mouse mutants have not been reported.

5. S1P5: S1P5, known previously as EDG-8 and lpB4, was the last of the S1P receptors to be cloned. It shows restricted tissue distribution to brain and spleen (Im et al., 2000a; Malek et al., 2001). Human S1P5 has 398 amino acids (Malek et al., 2001), and it has high sequence homology with other S1P receptors in other mammalian species. It couples to G\textsubscript{q}, G\textsubscript{q}, and G\textsubscript{12/13}. Deletion of this receptor alters natural killer cell trafficking (Walzer et al., 2007), and recent studies on another S1P5 constitutive null-mouse mutant (Jenne et al., 2009) indicated that this receptor influences immunological natural killer cell egress through a T-bet/Tbx21 transcription factor mechanism involving various immunological compartments. Its expression in oligodendrocytes of the CNS points to other possible roles that require further study.

### III. Lysophospholipid Receptor Agonists/Antagonists

#### A. Lysophosphatidic Acid Receptor Compounds

LPA receptor agonists include 1-oleoyl-2-O-methylracc-glycerophosphothionate (Hasegawa et al., 2003), with some selectivity for LPA\textsubscript{3}, fatty acid phosphates (Virag et al., 2003), and other possible agonist compounds (Jiang et al., 2007; Gajewiak et al., 2008). LPA receptor antagonists have been reported, with most compounds acting on LPA\textsubscript{1} and LPA\textsubscript{3}: 3-[[4-[[4-[[1-(2-chlorophenyl)ethoxy]carbonyl]amino]-3-methyl-5-isoxazolyl)phenyl]methyl]thio]-propanoic acid (Ki16425) (Ohta et al., 2003), (S)-phosphoric acid mono-[3-(4-benzyloxyphenyl)-2-octadec-9-enoylamino-propyl] ester (ammonium salt) (VPC12249), and related compounds (Heise et al., 2001; Okusa et al., 2003; Heasley et al., 2004a,b). The specificity of these agents, most of which are LPA analogs, must be re-examined in light of the discovery of additional LPA receptors. Investigations of LPA biology have been hampered by the lack of drug-like small molecules. Newer agents are under development by commercial entities targeting LPA signaling as a potential therapeutic target.

#### B. Sphingosine 1-Phosphate Receptor Compounds

The discovery that the immunosuppressant drug FTY720 (fingolimod) was converted by sphingosine kinase in vivo to a S1P mimetic that regulated lymphocyte trafficking by acting as an S1P1 agonist (Brinkmann et al., 2002; Mandala et al., 2002) spurred great interest in the development and use of S1P receptor-targeted compounds. FTY720-P is an agonist at the S1P1, S1P3, S1P4, and S1P5 receptors (Brinkmann et al., 2002, 2007; Mandala et al., 2002). There are now several relatively specific agonists and antagonists for most of the S1P receptors that have been used to investigate the physiologic roles of these
receptors in many biological systems. 5-{4-Phenyl-5-(trifluoromethyl)-2-thienyl}-3-[3-(trifluoromethyl)phenyl]-1,2,4-oxadiazole (SWE2871) is a specific agonist for S1P1 (Sanna et al., 2004). Lynch and Macdonald and colleagues have characterized the very useful VPC series: (R)-phosphoric acid mono-[2-amino-3-(4-oxetylphenylamino)]propyl ester (VPC 24191) and (R)-phosphoric acid mono-[2-amino-2-(6-octyl-1H-benzoimiazol-2-yl)-ethyl] ester (VPC 23153) are agonists at S1P1 and S1P3 (Clemens et al., 2003, 2004). N-(2,6-Dichloro-4-pyridinyl)-2-[1,3-dimethyl-4-(1-methylthethyl)-1H-pyrazolo[3,4-b]pyridin-6-yl]-hydrazinecarboxamide (JTE013) seems to be a specific antagonist at S1P2 (Osada et al., 2002; Sanchez et al., 2007). The (R)-3-amino-(3-hexylphenylamino)-4-oxobutylphosphonic acid (W146)/3-amino-4-(3-hexylphenylamino)-4-oxobutyl phosphonic acid (W140) chiral pair is very useful; W146 is an S1P1 antagonist and its enantiomer, W140, is an agonist at the same receptor (Gonzalez-Cabrera et al., 2008). Although still not well studied, it was reported that 2-undecyl-thiazolidine-4-carboxylic acid (CAY10444) is a specific S1P3 antagonist (Koide et al., 2007). The success of FTY720 in the clinic has spurred the search for similar molecules, particularly with S1P3 sparing activity. FTY720-like prodrugs include 2-amino-4-(2-chloro-4-(3-phenoxyphenyl)thio)phenyl-2-(hydroxymethyl)butyl hydrogen phosphate (KRP-203) (Shimizu et al., 2005) and 1-[1-amino-3-(4-oxetylphenyl)cyclopentyl]methanol (VPC01091) (Zhu et al., 2007) and are, after phosphorylation, agonists for S1P1, S1P2, and S1P5 but not S1P2 or S1P3. Numerous compounds that target S1P1 and S1P5 as direct agonists have been described previously (Li et al., 2005); most of these remain visible only in the patent literature.

C. Biological Functions of Lysophosphatidic Acid and Sphingosine 1-Phosphatase

An enormous literature has emerged in which LPA and S1P signaling has been implicated in most organ systems (for review, see Ishii et al., 2004; Gardell et al., 2006; Mutoh and Chun, 2008; Choi et al., 2010). This includes the nervous system (Ishii et al., 2004; Noguchi et al., 2009), immune system (Goetzl and An, 1999; Rubenfeld et al., 2006; Schwab and Cyster, 2007), reproductive system (Ye et al., 2005), and vascular system (Skouara and Hla, 2009; Teo et al., 2009). In addition, LPA, S1P, and their multiple receptors have been implicated in numerous human disease processes [many of which were noted in section II (Gardell et al., 2006)], including cancer (Mills and Moolenaar, 2003), fibrosis (Pradère et al., 2007; Tager et al., 2008), pain (Gardell et al., 2006), obesity (Simon et al., 2005; Yea et al., 2008), and, most importantly from the standpoint of a disease-modifying therapy in humans, multiple sclerosis (Chun and Hartung, 2010). Because most cell lineages in the body express at least one and usually several subtypes of these lysophospholipid receptors, the involved organ systems and disease processes are likely to expand in the near future.

V. Conclusions

Lysophospholipid receptors now constitute a validated group of GPCRs that, with the inclusion of LPAβ, comprise 11 different gene products. These receptors mediate both biological and pathophysiologic effects of LPA, S1P, and possibly other lysophospholipids as well. It is likely that additional receptors will be identified for these and possibly other classes of lysophospholipids. The broad scope of effects that have been reported in the literature underscores the upward trajectory of this field. The prospect of an actual medicine entering clinical practice on the basis of this receptor-based system—fingolimod as an oral medication for treating relapsing multiple sclerosis—raises the hope that new compounds and treatable therapeutic indications will be identified in the coming years.

Acknowledgments. This work was supported by the National Institutes of Health National Institute of Mental Health (Grant MH051699); the National Institute of Neurological Disorders and Stroke (Grant NS048478); the National Institutes of Health National Institute of Child Health & Human Development (Grant HD050685); the National Institutes of Health National Institute on Drug Abuse (Grant DA019674); the National Institutes of Health National Institute on Deafness and Other Communication Disorders (Grant DC009505) (all the preceding to J.C.); the National Institutes of Health National Institute of General Medical Sciences [Grants GM067958, GM052722 (to K.R.L.), GM043880 (to S.S.); the National Institutes of Health National Institute of Health, Lung, and Blood Institute [Grants HL67330, HL89934, HL70694] (to T.H.); the National Institutes of Health National Cancer Institute [Grant CA6177412] (to S.S.); the National Institutes of Health National Institute of Allergy and Infectious Diseases Extramural Activities [Grants AI50094, AI077435 (to J.C.); and the Dutch Cancer Society (to W.H.M.). We sincerely thank Drs. J. Aoki, S. Ishii, and G. Tigi for helpful discussions, along with our other colleagues whose important work has advanced this field, and we apologize for being unable to cite all relevant references. We thank D. Letourneau for editorial assistance. The authors are listed in alphabetical order.

REFERENCES

Castilla-Ortega E, Sánchez-López J, Hoyo-Becerra C, Mateos-Rico E, Zambrana-
LYSOPHOSPHOLIPID RECEPTOR NOMENCLATURE


The sphingosine-1-phosphate receptors S1P1, S1P2, and S1P3 function cooperatively during development and angiogenesis. J Biol Chem 278:25637–25642.


was deorphanized and shown to be a lysophosphatidic acid receptor. *Biochem Biophys Res Commun* **362**:861–866.


